LEPROSY—A CLINICAL AND PATHOLOGICAL CHALLENGE

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I SHOULD first wish to pay tribute to, and honour the memory of, a distinguished surgeon – a man of broad interests, a dogmatic teacher of no mean ability, an administrator with a social conscience. In this spirit, and conscious of the privilege that is mine of being invited to follow in this Lectureship some very eminent medical men, I make bold to suggest for consideration a topic that would have fascinated and intrigued its founder, A. B. Mitchell. From what I can gather, he enjoyed getting his teeth into problems that seemed at first sight too big for him.

The topic before us is: *"Leprosy – a clinical and pathological challenge"*. Before we consider what leprosy is, we should say what it is not, thereby removing some misconceptions and misunderstandings, and demolishing some cherished idols and pseudo-scientific folklore enshrined in medical text books and Bible dictionaries. Leprosy is not a highly contagious infection. It is not an invariably progressive disease, leading inevitably to mutilation and deformity. It is not a disease that is virtually incurable, one in which the fingers and toes drop off. It is not a mysterious condition somehow associated with Divine punishment for wrongdoing or ceremonial uncleanness, or with ritual defilement. It is not a condition invariably associated with poverty or beggary, or with dirt and squalor. It is not a fearful combination of the supposed incurability of cancer, the contagiousness of tuberculosis and the shame of venereal disease.

If leprosy is none of these things, what is it? It is a slightly contagious disease, caused almost certainly by a mycobacterium of low pathogenicity that has weak powers of invasion. It is usually self-limiting and self-healing. It is endemic in cold as well as in hot countries. It is characterized not only by disfiguring hypopigmented skin patches and nodules and by invasion of the mucosa of the upper respiratory tract, but also pre-eminently and most importantly by damage to the peripheral nerves. It is not necessarily associated with dirt, poverty, overcrowding or poor hygiene, although each of these factors may have something to do with its spread, or with its persistence in any one focus. It is, of course, unassociated with venereal transmission, and should bear no connotation of shame.

Clinically and pathologically, leprosy is several conditions, and as such it presents a continuing challenge to those interested in disease and sequelae of disease, in human suffering and in economic loss. It is, firstly, an infection by *Mycobacterium leprae* of the dermis, the mucosa of the upper respiratory tract and the peripheral nerves. It is of insidious onset, and the source of infection is often unknown. The disease itself is characterized by extremely slow progress. Leprosy is

not a very serious disease from the public health standpoint : it does not appear in sudden epidemics, and it carries no high mortality.

Leprosy, however, is not only a mycobacterial infection: it represents, secondly, the summation of a variable cellular response to infection. On the one hand, bacilli may be very scanty, multiplying apparently with great difficulty; the presence of rare bacilli is accompanied by a vigorous cellular reaction. On the other hand, there may be an enormous parasitization of the reticulo-endothelial cells of the dermis, and a bacillary invasion of all the peripheral nerves. It is the host-response to the infection that determines the nature of the clinical disease.

In the third place, leprosy represents the mechanical – rather than the toxic – effects of this response. Tuberculoid leprosy is characterized histopathologically and clinically by a progressive destruction by fibrosis of sweat glands, pigment-forming cells of the basal layer of the epidermis, hair follicles, nerve endings and nerve fibres; at length, when the granuloma involves the reticular layer, the fibrotic constriction of important structures leads to functional ablation. This latter type of destruction occurs, for example, in a superficial nerve immediately subjacent to a minor tuberculoid lesion, and necessarily partakes in the localized fibrosis following a vigorous cellular response to paucibacillary infection; or in the nasal duct involved in a progressive fibrotic process with consequential epiphora and ulceration of the facial skin. Extremely numerous bacilli may be aggregated together in masses of Virchow, lepra or foamy cells, the whole protruding as a lepromatous nodule. Such masses of highly bacilliferous granulomata may be present diffusely in the dermis or in the mucosa of the upper respiratory tract. There are smaller and clinically less important aggregations in the liver, the bone marrow and the spleen.

It is in the peripheral nerves that the fibrosis following degeneration of mycobacteria has its most serious and far-reaching consequences. Enormous numbers of viable and morphologically normal mycobacteria may exist and multiply between the fibres of the peripheral nerves without provoking an inflammatory response, but when these bacilli degenerate and attract an outpouring of lymphocytes with an accompanying oedema, nerve pathways may be temporarily interrupted or permanently destroyed.

In the fourth place, leprosy may be regarded as the peripherally distant results of this temporary or irreversible damage to nerve fibres; these results primarily interest the surgeon – the plastic and orthopaedic surgeon, and the ophthalmic surgeon. Partial pareses and complete paralyses develop in the intrinsic muscles of the hands and feet, and in the facial muscles. Paraesthesiae and areas of numbness that are persistent or localized or recurrent, may precede total sensory anaesthesia. The first modality to be lost is usually that of light touch. Heat and cold soon follow, and then pain. The deep reflexes are usually retained, as are muscle and joint sense and vibration sense in bone. Notwithstanding the very extensive and severe sensory loss, stereognosis is often retained to a surprising degree. Changes may occur in the calibre of blood vessels, in local reflexes on stimuli, in pigment formation and in sweating in the direction of hypo- or hyper-idrosis.

In the fifth place, leprosy may be regarded as demonstrating the phenomena of tissue sensitization, or as the manifestations of an antigen-antibody reaction. In this respect leprosy has many features suggestive of auto-immune disease, and its

neuropathy is reminiscent of the polyneuritis of Guillain-Barré. Other possible examples of hypersensitive phenomena are to be seen pre-eminently in the iris and ciliary body, and in the subcutaneous tissues; in the latter the manifestations may be classed as those of erythema nodosum leprosum, the lesions of which may be discrete and acuminate, or a more diffuse, generalized and coalescent panniculitis. This is accompanied in severe cases by inflammation of the lymph nodes, by polyarthritis going on to effusion into the medium-sized joints, by acute anaemia and gynaecomastia, sometimes associated with orchitis and testicular atrophy. Such systemic symptoms as pyrexia, severe malaise, and pain in nerves, muscle masses and joints, coupled with the presence of C-reactive protein in the serum, cryoproteins, increased gamma-globulin, and (occasionally) LE cells – all suggest some complex disturbance of the body response-system.

Lastly, leprosy may be regarded not only as any or all of the above manifestations of a disease process, but also as an attitude of mind – in the patient and his entourage, in society, in governments and legislative bodies. There are countries where this aspect of leprosy is its most important feature, outweighing in seriousness the controllable contagion caused by *Myco. leprae*. Attitudes, misconceptions and prejudices are often more difficult to change and eradicate than physical entities.

Wherein lies the clinical challenge of leprosy?

Leprosy is overlooked or wrongly diagnosed, with great frequency. The time-lag between the first sign and correct diagnosis is often several years. Since all patients at present under treatment in Great Britain have contracted the disease abroad, leprosy should be considered in the differential diagnosis of any dermatosis or neuropathy in anybody who has travelled out of the country, and especially in contacts of known cases. We should think of leprosy when faced with any obscure dermatosis – or any chronic non-irritating skin condition that either does not resemble one of the commoner categorized dermatoses or fails to respond to usually effective treatment. A peripheral neuritis whose aetiology is not apparent, and especially if accompanied by some kind of skin rash, may be due to leprosy.

The positive signs of diagnosis of leprosy may be summarized as follows: a localized area of skin showing altered pigmentation, impaired tactile sensibility, loss of sweating, disturbance of hair growth, and, of course, the presence of *Myco. leprae*. If the practitioner awaits all these conditions – or the majority – he will fail to diagnose early leprosy and even the advanced disease. The earliest stages may be represented by vague prodromal symptoms of paraesthesiae, evanescent lesions and, very importantly, self-healing lesions.

The second aspect of the clinical challenge of leprosy concerns the differential diagnosis of the disease. This is too vast a subject to discuss fully. Leprosy may be – and very often is – confused with almost any dermatosis, with congenital conditions, with skin infections and neoplasms. One very common neurological sign in leprosy, almost pathognomonic, is frequently overlooked. The peripheral nerve trunks, especially at sites of predilection, where they course superficially or near joints, are enlarged and hard and tender. This sign, confined to one nerve or present in all the main peripheral nerve trunks, is encountered very infrequently in such rarities as: generalized amyloidosis of nerves, and Déjerine Sotta's disease (Thevenard's syndrome, or congenital hypertrophic familial polyneuritis). In cases of congenital indifference to pain, the nerve trunks are clinically normal.

The third aspect of this challenge concerns the acute exacerbation of lepromatous leprosy, characterized by a more or less sudden appearance, and a more or less prolonged persistence, of features of the hypersensitive state. Many fundamental questions concerning pathogenesis and treatment remain unanswered. In the case of acute irido-cyclitis, or sudden widespread and severe polyneuritis, the clinical results are serious and may be permanent.

The fourth aspect of this challenge concerns the nerve damage in leprosy. Why the predilection for peripheral nerves, and the sparing of the central nervous system? Why the damage to certain modalities, or to certain levels of the nerve? The clinical impairment may be mainly motor or mainly sensory, or any combination of the two and to any degree. The affection may be transient or permanent. The auto-sensitization of nerve tissue by products of nerve damage, and the enhancement of a non-specific effect by extracts obtained from other mycobacteria, are two aspects of this problem that may have important bearings on the pathogenesis of auto-immune disease in general.

These considerations have a bearing on the practical problems confronting the surgeon, problems such as acute foot-drop, sudden orbicularis paralysis, other paralyses, deformities, contractures, ulceration of anaesthetic extremities, etc. All these conditions would be preventible if only leprosy were diagnosed early and treated properly. Moreover, at whatever stage active leprosy is encountered in the individual patient, further damage to nerves and the consequences of such damage may be corrected by judicious application of known surgical principles.

An indispensable adjunct to surgery is physiotherapy; in point of fact, the actual surgical intervention may be regarded as an interlude in the prolonged and exacting task of the physiotherapist who not only aims at restoring paresed muscles to useful function and re-educating the patient, e.g., after tendon-transfer operations, but who plays an important role in counselling the patient to care for his anaesthetic extremities.

Another valuable member of the team is the shoemaker, who utilizes locally available materials and locally available skills to produce cheap and durable and acceptable protective footwear. The splint and brace-maker and the prosthetist complete the team as far as physical restoration and rehabilitation are concerned.

The damage done by leprosy, however, must be considered also in relation to its mental, social and even its spiritual aspects. These together constitute a tremendous challenge to those whose objective is the restoration of the individual sufferer to integrity and usefulness as a person in his community.

The Pathological Challenge

The problems in leprosy awaiting solution are of importance not only to the study of leprosy itself and to related mycobacterial infections, but also to general medicine and surgery, to epidemiology, immunology and bacteriology. Their solution depends in turn upon advances in related branches and upon the utilization of modern investigative aids and tools. The cross-fertilization of ideas that produces results could come from research workers now tackling problems in related disciplines (such as tuberculosis or auto-immune disease). In the past, leprologists have unfortunately been isolated and segregated from their fellows. Let us glance briefly at some of these pathological challenges.

Firstly, although the leprosy bacillus was one of the first micro-organisms to be cited as the cause of human disease, it has not yet been cultured *in vitro*.

Secondly, until recently it has been impossible to reproduce in the experimental animal a generalized progressive granulomatous disease.

Thirdly, the fundamental questions of resistance and susceptibility await solution : the exact significance of the Mitsuda test in this connection is still obscure, and potential response to mycobacterial antigen injected intradermally may not also indicate potential resistance if the subject should be challenged by leprosy infection.

In the fourth place, the transmission of leprosy provides another series of pathological problems still unsolved. The sole orthodox nidus of *Myco. leprae* is human tissue, but its existence in fomites or its persistence after being shed outside the human body has not been demonstrated. Viral forms or L-forms may indeed exist, whose importance in the transmission of leprosy is quite unsuspected. The actual inoculation and implantation of the bacillus also provides many unanswered questions. The long silent, or latent, or incubation period of several years awaits elucidation. (A partial explanation, of course, resides in the prolonged generation time of this bacillus, probably a matter of two or three weeks). Why does the leprosy bacillus invade the tissues apparently with ease in some patients and fail to establish itself in others? Is susceptibility genetically determined? Does it depend upon an initial unnoticed inoculation, which results in a tissue hypersensitivity? Is a positive lepromin test associated with infection by related mycobacteria, named or anonymous?

In the fifth place, skin hypersensitivity in leprosy has intriguing parallels with granulomata produced by beryllium, zirconium and silicon, and with antigenic extracts of liver, skin, etc.

Then there is the range of sarcoid phenomena in lymph nodes, skin, eye, bone, etc. Other mycobacterial infections show some resemblances to the chronic granulomata caused by or associated with *Myco. leprae* : tuberculosis, swimming-bath granuloma, Buruli ulcer (*Myco. ulcerans sp.*), Stefansky's infection in rodents, and infection by related mycobacteria in water buffalo, wood-pigeons, salmon, frogs, snakes, etc.

I may now refer to recent experimental work that is furnishing some long-awaited answers to these and other questions. The inoculation of leprosy bacilli into the footpad of the mouse will result in mathematically demonstrable multiplication of the bacilli after a prolonged period (to be correlated with the prolonged generation time of the bacillus). This elegant demonstration of a localized bacillary multiplication is not to be confused with generalized mycobacterial granulomatous disease, but it does provide definite evidence that *Myco. leprae* is viable and can multiply within the special conditions of the biological experiment.

This technique is now being used as a screening procedure, to demonstrate the activity of drugs, drug-resistance, and the enhancement of resistance to leprosy by B.C.G. inoculation. The minimal inhibitory doses of standard drugs employed in leprosy can be determined, and, in fact, the method has shown that such drugs as dapsone and B 663 (Geigy), a phenazine derivative, are potent in extremely low concentrations.

It has recently been demonstrated that thymectomized mice who have been

exposed to high doses of whole body irradiation (900 r) will develop a generalized granulomatous disease after inoculation with *Myco. leprae*. The granulomatous masses contain morphologically normal *Myco. leprae* surrounded by a cellular exudate and infiltration that is comparable with that seen in the human subject with lepromatous disease.

Much work is also proceeding on the changes in the serum consequent upon leprosy infection. The gamma-globulins are increased, and cryoproteins have been recently demonstrated. This subject presents a considerable challenge to the biochemist and the immunologist. The common antigenic pattern of several related mycobacteria has been demonstrated by biochemical and immunological methods.

Conclusion and Summary

Such is leprosy, one of the earliest human infections to be associated with a specific micro-organism – and one of the latest to yield its secrets to research. Surrounded by more superstitution and prejudice than any other condition known to medical science, leprosy still constitutes a tremendous challenge, clinically and pathologically, scientifically and socially. It is the world's greatest crippler, yet it has received but scant notice on this count. It is the last of the great infectious endemics to reveal its mode of transmission and many of its epidemiological secrets. Although five millions have been cured of leprosy within the last twenty years, there are fifteen millions who suffer today, and within the next five years another million will probably develop leprosy and another quarter of a million will become crippled because of leprosy. This constitutes a clinical and pathological challenge that would have stirred the scientific and humanitarian heart of A. B. Mitchell.

N.B. Rather than overload the lecture with numerous references to the literature, I would direct attention to recent issues of *The International Journal of Leprosy and other Mycobacterial Diseases*, *Leprosy Review*, and the monthly abstracts and annual reviews appearing in *Tropical Diseases Bulletin*. Nearly all significant research work in leprosy finds its way into one or other of these publications.